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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,516	03/27/2006	Daniel Bur	AC-43-US	4476

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EXAMINER	
MABRY, JOHN	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
06/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,516	BUR ET AL.	
	Examiner	Art Unit	
	JOHN MABRY	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,8-11,14,17-22 and 25-28* is/are pending in the application.

4a) Of the above claim(s) *3,4,6,7,12,13,15,16,23,24 and 32-37* is/are withdrawn from consideration.

5)☒ Claim(s) *26 and 27* is/are allowed.

6)☒ Claim(s) *1,2,5,8-11,14,17-22,25 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/27/06; 4/22/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Examiner's Response

Applicant's response on February 23, 2009 filed in response to the Election/Restriction dated January 22, 2009 has been received and duly noted. The Examiner acknowledges Applicants' election of Group III with traverse.

The Applicant requested clarification of restricted groups with respect to "n". Examiner inadvertently restricted groups to "n" being 1 and 2. Examiner intended to restrict groups where n is 0 and 1. The revised restriction requirement is reflected below that addresses this issue.

I. Claims 1, 2, 3, 4, 10, 11, 12, 13, 18, 19, 20, 23, 24, 25, 26 (in-part), 27 (in-part) and 28 are drawn to compounds and pharmaceutical compositions of Formula I, wherein n=1, X= aryl; aryl-C_{1-7}-alkyl-;. A further election of single disclosed species is required.

II. Claims 1, 2, 9, 10, 11, 18, 19, 20, 25, 26 (in-part), 27 (in-part) and 28 are drawn to compounds and pharmaceutical compositions of Formula I, wherein n=1, X= aryl-O-; aryl-C_{1-7}-alkyl-O-;. A further election of single disclosed species is required.

III. Claims 1, 2, 5, 8-11, 14, 17-22, 25, 26 (in-part), 27 (in-part) and 28 are drawn to compounds and pharmaceutical compositions of Formula I, wherein n=1, X= R^1-SO_2NR^2-; R^1-$CONR^2$-; aryl-R^6-$CONR^2$-; R^1-NR^3CONR^2-;. A further election of single disclosed species is required.

IV. Claims 1, 2, 6, 7, 9, 10, 11, 15, 16, 18, 19, 20, 25, 26 (in-part), 27 (in-part) and 28 are drawn to compounds and pharmaceutical compositions of Formula I, wherein n=1, X= R^1-NR^2CO-. A further election of single disclosed species is required.

V. Claims 1, 2, 9, 10, 11, 18, 19, 20, 25, 26 (in-part), 27 (in-part) and 28 are drawn to compounds and pharmaceutical compositions of Formula I, wherein n=1, X= X and Z represent together with the carbon atom to which they are attached an exocyclic double bond which bears an aryl substituent at the thus formed methylene group; . A further election of single disclosed species is required. The group may be subject to further restriction if chosen.

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VI. Claims 1, 2, 3, 4, 10, 11, 12, 13, 18, 19, 20, 23, 24, 25, 26 (in-part), 27 (in-part) and 28 are drawn to compounds and pharmaceutical compositions of Formula I, wherein n=0, X= aryl; aryl-C_{1-7}-alkyl-. A further election of single disclosed species is required.

VII. Claims 1, 2, 9, 10, 11, 18, 19, 20, 25, 26 (in-part), 27 (in-part) and 28 are drawn to compounds and pharmaceutical compositions of Formula I, wherein n=0, X= aryl-O-; aryl-C_{1-7}-alkyl-O-. A further election of single disclosed species is required.

VIII. Claims 1, 2, 5, 8-11, 14, 17-22, 25, 26 (in-part), 27 (in-part) and 28 are drawn to compounds and pharmaceutical compositions of Formula I, wherein n=0, X= R^1-SO_2NR^2-; R^1-$CONR^2$-; aryl-R^8-$CONR^2$-; R^1-NR^3CONR^2-;. A further election of single disclosed species is required.

IX. Claims 1, 2, 6, 7, 9, 10, 11, 15, 16, 18, 19, 20, 25, 26 (in-part), 27 (in-part) and 28 are drawn to compounds and pharmaceutical compositions of Formula I, wherein n=0, X= R^1-NR^2CO-;. A further election of single disclosed species is required.

X. Claims 1, 2, 9, 10, 11, 18, 19, 20, 25, 26 (in-part), 27 (in-part) are drawn to compounds and pharmaceutical compositions of Formula I, wherein n=0, X= X and Z represent together with the carbon atom to which they are attached an exocyclic double bond which bears an aryl substituent at the thus formed methylene group;

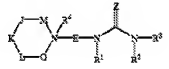
A further election of single disclosed species is required. The group may be subject to further restriction if chosen.

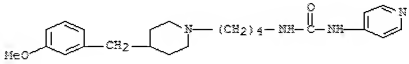
XI. Claims 32-37 are drawn to a method of treating a patient suffering from urotensin II and urotensin II receptors and associated diseases and conditions limited to the scope of one of groups I - X. An election of species is required if this group is chosen.

Note: The revised restriction is based upon claims as originally filed.

The Applicant requested the withdrawal of the Restriction Requirement arguing that Ko et al does not specifically disclose a compound have a pyridine-4-yl ring substituted at the 2 and 6 positions. Examiner respectfully disagrees.

As previously communicated in Restriction Requirement, Ko et al (6,331,541) discloses the technical feature linking these inventions is the common core found in Formula I. US '541 as describes genus and species below. Applicant argues that Ko et al does not disclose pyridine-4-yl ring substituted at the 2 and 6 positions and that variable X of the current set of claims has been amended. However, Ko et al teaches that the pyridine-4-yl ring (which corresponds to R3 of Ko's genus below) can be substituted with 0-5 substituents (see R3, column 5, lines 15-19) with C1-C8 alkyls (see column 9, lines 26-27). Thus Applicant's invention as originally disclosed is not a contribution over the prior art.





Examiner's Election/Restriction was properly restricted, thus, the restriction requirement is deemed proper and **FINAL**.

DETAILED ACTION

Specification Objections

The title of the invention is objected to. The current title contains the term "Novel". The novelty of the invention is decided by the USPTO, not the Applicant. It is recommended that this term be deleted.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 recites variable R4 and R5, but Applicant has deleted said variables from variable Z within claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 9-11, 18-20, 25 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 9-11, 18-20, 25 and 28 recite the limitation "R4 and R5". "R4 and R5", has been deleted from variable Z. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5, 8-11, 14, 17-22, 25 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R6 and R7 being H and aryl where applicable in **all claimed instances** being enabled for phenyl optionally substituted with (a) NHAc, haloalkyl, halogen, alkyl, alkoxy, (b) thiophenyl optionally substituted with halogen, and unsubstituted pyridinyl does not reasonably provide enablement for R6 and R7 and aryl **all claimed instances** being the full scope as claimed.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims: Scope of the compounds. Owing to the range of many variables, millions of highly substituted pyridine piperidinyl compounds are embraced.

(2) The nature of the invention: The invention is a highly substituted pyridine piperidinyl compounds.

(3) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and chemical reactivity (which is affected by determinants such as substituent effects, steric effects, bonding, molecular geometry, etc) is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(4) Direction or Guidance: That provided is very limited. Applicant shows a general synthesis of compounds of application's general formula I. The Specification describes starting materials and methods for synthesis of compounds wherein aryl is phenyl, pyridinyl and thiophenyl and R6 and R7 is H, but does not describe or list any reagents wherein compounds can be used to synthesis compounds where said variables as listed above. There is limited evidence in the Specification of the example compounds that only covers no or a small portion of the substituents claimed of formula. Thus, there is no specific direction or guidance regarding said compounds specifically mentioned in Scope.

For instance, the specification does not provide any support for the synthesis of compounds, for the full scope of aryl as claimed. Applicant's definition of "aryl" is shown below and as shown on page 5 of Specification.

> The term 'aryl' means a substituted or unsubstituted aromatic carbocyclic or heterocyclic ring system, consisting of a five- or six- membered aromatic ring, or of a fused five-six or six-six aromatic ring system.

According to Applicant's definition of the term "aryl", an infinite number of substituted aromatic carbocyclic and heterocyclic ring systems are possible. Applicant's showing of only three of the infinite number of possibilities deems the claimed invention as not being enabled.

The availability of the starting material that is needed to prepare the invention as claimed is at issue here...As per MPEP 2164.01 (b). A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to a make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court *in re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made it clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

It is not trivial to experimentally interchange any and all of the many substituents that exist. As generally described by F. Zaragoza Dörwald, most organic syntheses fail initially and chemical research is highly inefficient due to chemists spending most of their time "finding out what went wrong and why". Therefore, most syntheses of organic

compounds are labor-intensive and demanding. Additionally, most final synthetic routes to desired organic molecules are usually very different from initially planned routes. A highly skilled chemist can agree that for many successful organic compounds made, many failures are encountered and experimental repetition is common. This also contributes to the burden and unpredictability of the syntheses of said compounds. (see "Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design" 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

(6) Working Examples: Applicant shows examples where aryl is phenyl, thiophenyl and pyridinyl and R6 and R7 being H but no working examples for the full scope of R6 and R7 and aryl.

(7) Skill of those in the art: The ordinary artisan is highly skilled, e.g. a masters or PhD level chemist.

(8) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome.

Due to the level of unpredictability in the art, the very limited guidance provide, and the lack of working examples, the Applicant has not provided sufficient guidance for the artisan to make the invention.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/
Examiner
Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625